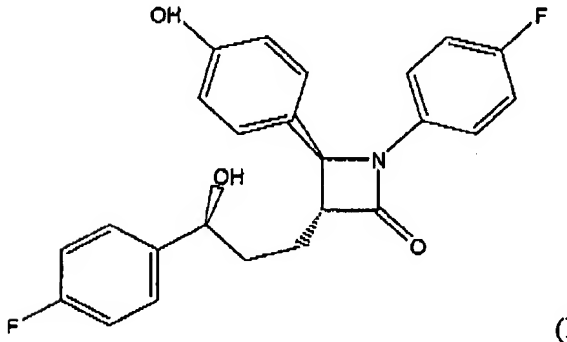
REMARKS

Claims 1, 35-37, 42, 45 and 47 are pending in this application. Claims 4-10, 12-17, 21-34, 38-41, 46 and 48 have been withdrawn by the Examiner. Claims 2, 3, 11, 18-20, 43-44 and 46 were canceled, without prejudice to filing of one or more divisional or continuation applications directed to the canceled subject matter.

The Office Action asserts a rejection against all of the pending claims in this application under 35 U.S.C. § 103. In summary, the rejection asserts that the pending claims are purportedly unpatentable over Rosenblum *et al.* (EP 0720599) and Ullah (WO 99/47123) in view of Frei (Proc. Soc. Exp. Biol. Med. 1999 Dec; 222(3): 196-204). Applicants respectfully traverse this rejection for the reasons discussed below.

In embodiments set forth in claims 1 and 47, Applicants have discovered compositions and combinations comprising:

(a) at least one sterol absorption inhibitor represented by Formula (II):



(II)

isomers, prodrugs, or pharmaceutically acceptable salts or solvates thereof; and

(b) aspirin.

Ezetimibe (Formula II) is the active ingredient in ZETIA® pharmaceutical formulation, which is commercially available from MSP (Merck Schering-Plough) Pharmaceuticals, Inc. See Response to Restriction Requirement and Election of Species of September 9, 2003 ("Response"). In the same Response, Applicants provisionally elected with traverse aspirin as the blood modifier and simvastatin (an HMG CoA reductase inhibitor) as the third therapeutic agent.

The claimed compositions, combinations and treatment methods can be useful for treating vascular conditions and/or lowering concentration of a sterol in plasma in a mammal (page 72, lines 13-18 of the specification).

On January 9, 2007, Applicants submitted for consideration a Declaration by Harry Davis, Jr., Ph.D. dated January 3, 2007, ("Davis Declaration"). Dr. Davis has a Bachelor of Science in Animal and Veterinary Science degree from the University of Maine (1977), Master of Science in Anatomical Pathology degree from George Washington University (1979) and a Doctorate Degree in Pathology from the University of Chicago (1982). (Davis Declaration at paragraphs 1-3).

Dr. Davis is employed by Schering-Plough Research Institute ("Schering") as a Distinguished Research Fellow in the field of Cardiovascular and Metabolic Disease and has been employed in this capacity since 1993 and was previously employed by Schering as a Principal Scientist since November 1987. (Davis Declaration at paragraph 4). Dr. Davis' duties at Schering have included pharmaceutical drug discovery and basic research in lipid absorption and metabolism and metabolic disease. (Davis Declaration at paragraph 5).

As discussed in Dr. Davis' Declaration, hypercholesterolemia has been associated with an increased sensitivity for platelets to aggregate and cause vascular complications. (Davis Declaration at paragraph 6). A study was conducted under Dr. Davis' supervision to determine if a reduction in plasma cholesterol levels by ezetimibe (EZ) would enhance the ability of aspirin (ASA) to act as a platelet aggregation inhibitor. (Davis Declaration at paragraph 6).

Rats were fed a 1% cholesterol + 0.5% cholate diet (HC) alone or containing ezetimibe (0.0036%, 3 mg/kg/day) for 7 days. (Davis Declaration at paragraph 6). On day 7 they were treated with aspirin at 100 mg/kg or vehicle, and platelet aggregation determined. (Davis Declaration at paragraph 6). Mean plasma cholesterol levels were reduced from 344 ± 22 mg/dl to 60 ± 4 mg/dl by ezetimibe treatment. (Davis Declaration at paragraph 6). Platelet aggregation by adenosine diphosphate (ADP) and collagen was not altered, as expected, among the groups. (Davis

Declaration at paragraph 6). Arachidonic acid (AA) induced platelet aggregation at 0.3 mM was increased by the hypercholesterolemic diet compared to normal chow fed rats (Table), indicating an increased sensitivity to aggregate with hypercholesterolemia. (Davis Declaration at paragraph 6). AA induced aggregation was not reduced in the aspirin alone treated hypercholesterolemic animals. (Davis Declaration at paragraph 6). **AA induced aggregation was reduced in the aspirin + ezetimibe treated rats compared to the aspirin alone treated hypercholesterolemic rats** (Table). (emphasis added) (Davis Declaration at paragraph 6).

Table: Platelet Aggregation

Agonist	Regular Chow	High Cholesterol (HC) diet	HC + EZ	HC + ASA (100 mpk)	HC + EZ + ASA (100 mpk)
AA (0.3 mM)	7 ± 3	14 ± 2	13 ± 2	12 ± 2	7 ± 2
AA (1 mM)	16 ± 2	17 ± 3	16 ± 3	14 ± 2	5 ± 2
ADP (10 µM)	24 ±1	21 ± 2	21 ± 3	25 ± 2	31 ± 1
Collagen (3 µg/ml)	25 ± 1	24 ± 3	27 ± 3	30 ± 2	32 ± 1

Aggregation in whole blood (ohms)
N=6 per group, Mean ± SEM

In Dr. Davis' opinion, these results indicate that the combination of ezetimibe with aspirin enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. (Davis Declaration at paragraph 6). *The above test data provide evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone.*

Also, on January 9, 2007 Applicants submitted for consideration the Declaration by Madhu Chintala, Ph.D. dated January 4, 2007 ("Chintala Declaration"). Dr. Chintala has a Bachelor of Science degree in Zoology from the University of Madras, India (1984), Master of Science degree in Ocean Life Sciences from the University of Madras, India (1985) and a Doctorate Degree in Pharmacology from the University of Houston (1991). (Chintala Declaration at paragraphs 1-3).

Dr. Chintala has been employed by Schering-Plough Research Institute ("Schering") as an Associate Director in the field of Cardiovascular and Metabolic Disease since 2003 and was previously employed by Schering as a scientist since 1991. (Chintala Declaration at paragraph 4). Dr. Chintala's duties at Schering have included

pharmaceutical drug discovery and basic research in the areas of atherothrombosis, heart failure, lipid disorders and metabolic diseases. (Chintala Declaration at paragraph 5).

The above platelet aggregation study was also conducted under the supervision of Dr. Chintala. (Chintala Declaration at paragraph 6).

In his Declaration, Dr. Chintala discussed the rationale for dose selection of aspirin and ezetimibe for the above study in rats, as follows. (Chintala Declaration at paragraphs 7-9). Aspirin is an antiplatelet agent which is widely used to prevent atherothrombosis in the treatment of cardiovascular disorders including stroke. (Chintala Declaration at paragraph 7). Aspirin exerts its beneficial effects by inhibiting platelet aggregation and thrombus formation also commonly referred to as blood clots. (Chintala Declaration at paragraph 7). Ex-vivo platelet aggregation (a measure of platelet function) has widely been used as a surrogate for antithrombotic activity and for determining the therapeutic doses of aspirin in humans and in animals. (Chintala Declaration at paragraph 7).

The dose of aspirin used clinically to treat patients varies depending on the indication/disease conditions. (Chintala Declaration at paragraph 7). A standard dose of 100 mg/day was shown sufficient to inhibit platelet aggregation in 90% of patients in primary and secondary prevention of cardiovascular diseases.[1] (Chintala Declaration at paragraph 7). Doses of 300 and 600 mg/day were required in stroke patients with single or recurring events.[2] (Chintala Declaration at paragraph 7). Higher doses of 500-1000 mg were found effective in the treatment of fever and other symptoms of upper respiratory tract infection in adults,[3] in the treatment of episodic tension-type headache,[4] and to prevent platelet activation in patients before and after percutaneous coronary

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[1] Syrbe *et al.*, *Individual Dosing of ASA Prophylaxis by Controlling Platelet Aggregation*, Clin. Appl. Thromb. Hemost. Jul; 7(3): 209-13, 2001 (Abstract only).
[2] Chamorro *et al.*, *Ex Vivo Response to Aspirin Differs in Stroke Patients with Single or Recurrent Events: A Pilot Study*, J. Neurol. Sci. Dec 15; 171(2): 110-4, 1999.
[3] Bachert *et al.*, *Aspirin Compared with Acetaminophen in the Treatment of Fever and Other Symptoms of Upper Respiratory Tract Infection in Adults: A Multicenter, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, Single-Dose, 6-Hour Dose-Ranging Study*, Clin. Ther. Jul; 27 (7): 993-1003, 2005.
[4] Steiner *et al.*, *Aspirin in Episodic Tension-Type Headache: Placebo-Controlled Dose-Ranging Comparison with Paracetamol*, Cephalalgia, Feb; 23 (1): 59-66, 2003.

interventions.[5] (Chintala Declaration at paragraph 7). In Dr. Chintala's opinion, the dose of aspirin varies in humans depending on the clinical indication and it is reasonable to assume that the therapeutic range is from 1-1000 mg. (Chintala Declaration at paragraph 7).

In the above rat studies, Dr. Chintala used aspirin at 100 mg/kg, orally. (Chintala Declaration at paragraph 8). In Dr. Chintala's experience, this dose of aspirin is necessary to inhibit platelet aggregation in rats 1-2 hrs after oral dosing. (Chintala Declaration at paragraph 8). Studies in the literature have employed different doses of aspirin in rats and the dose varies upon the route of administration and the type of injury/thrombosis model used. (Chintala Declaration at paragraph 8). In a rat model of laser-induced thrombosis, administration of aspirin at 100 mg/kg prevented thrombus formation.[6] (Chintala Declaration at paragraph 8). In a similar laser-injury model, Vesvres *et al.* (1993) have shown that doses of 50, 100 and 200 mg/kg, administered intramuscularly prevented thrombus formation in a dose dependent manner.[7] (Chintala Declaration at paragraph 8). Killackey *et al.* (1984) have reported that they required 200 mg/kg of aspirin to prevent carotid artery thrombosis in a rat model and that the 100 mg/kg dose was insufficient.[8] (Chintala Declaration at paragraph 8). In contrast, several reports have shown that doses of aspirin ranging from 1-50 mg/kg did not significantly inhibit thrombus formation in rats[9,10] or they had modest effects.[11,12] (Chintala Declaration at paragraph 8). Thus, the therapeutic dose of aspirin in rats is around 100

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[5] ten Berg *et al.*, *High-Dose Aspirin in Addition to Daily Low-Dose Aspirin Decreases Platelet Activation in Patients Before and After Percutaneous Coronary Intervention*, Thromb. Res. Mar; 105 (5): 385-90.
[6] Aguejouf *et al.*, *Effects of Acetyl Salicylic Acid Therapy on an Experimental Thrombosis Induced by Laser Beam*, Thromb. Res. Sep 15; 99(6): 595-602, 2000.
[7] Vesvres *et al.*, *Effects of Aspirin on Embolization in an Arterial Model of Laser-Induced Thrombus Formation*, Haemostasis. 23(1): 8-12, 1993 (Abstract only).
[8] Killackey *et al.*, *The Effects of High Doses of Aspirin and Related Benzoic Acid Derivatives on Arterial Thrombosis in Male Rats*, Haemostasis. 14(4): 354-60, 1984 (Abstract only).
[9] Schumacher *et al.*, *Superior Activity of a Thromboxane Receptor Antagonist as Compared with Aspirin in Rat Models of Arterial and Venous Thrombosis*, J Cardiovasc Pharmacol. Oct; 22(4): 526-33, 1993.
[10] Lockyer *et al.*, *Demonstration of Flow and Platelet Dependency in a Ferric Chloride-Induced Model of Thrombosis*, Cardiovasc Pharmacol. May; 33(5): 718-25, 1999.
[11] Hirose *et al.*, *Antiplatelet and Antithrombotic Effects of a Novel Selective Phosphodiesterase 3 Inhibitor, NSP-513, in Mice and Rats*, Japanese J Pharmacol. Mar; 82(3): 188-98, 2000 (Abstract only).
[12] Schumacher *et al.*, *A Ferret Model of Electrical-Induction of Arterial Thrombosis That is Sensitive to Aspirin*, J Pharmacol Toxicol Methods. Feb; 35(1): 3-10, 1996.

mg/kg. (Chintala Declaration at paragraph 8). Therefore, in Dr. Chintala's opinion, the dose used in the above studies in the therapeutic range for prevention of thrombosis in rats is consistent with reports in the literature. (Chintala Declaration at paragraph 8). While on an mg/kg basis, the dose of aspirin used in the above studies (100 mg/kg in rats) is much higher than the 1-1000 mg/day (total dose) in humans, it is still in the therapeutic range for rats. (Chintala Declaration at paragraph 8). The reason for the difference in dose from rats to humans can be due to multiple factors influenced by the absorption, metabolism and elimination of the aspirin, and is not clearly understood. (Chintala Declaration at paragraph 8).

In the above study, rats were dosed with ezetimibe at 3 mg/kg/day, which was previously found to be the maximally effective dose to prevent diet-induced hypercholesterolemia in rats.[13] (Chintala Declaration at paragraph 9). Therefore, in Dr. Chintala's opinion, doses ranging from 0.1-1000 mg of ezetimibe/day, with the usual dose of 10 mg of ezetimibe/day, should be effective clinically in humans. (Chintala Declaration at paragraph 9).

At pages 2-5 of the Office Action, claims 1, 35-37, 42, 45 and 47 were rejected under 35 U.S.C. §103(a) as purportedly unpatenable over EP 0720599 ("Rosenblum *et al.*") and WO 99/47123 ("Ullah") in view of Frei (Proc Soc Exp Biol Med. 1999 Dec. 222(3): 196-204). In the Office Action, it was alleged that Rosenblum *et al.* disclosed that compositions including the compound of Formula II can be combined with HMG CoA reductase inhibitors such as simvastatin to reduce cholesterol and risk of atherosclerosis (Office Action at page 3). Ullah was cited as teaching a composition comprising statins, such as simvastatin, in combination with aspirin, for cholesterol lowering and treating or reducing the risk of developing atherosclerosis (Office Action at page 3).

It is acknowledged in the Office Action that the primary references do not expressly teach the claimed composition comprising the compound of Formula II (ezetimibe), aspirin and simvastatin together or that antioxidants be incorporated into

[13] van Heek *et al.*, *Ezetimibe Potently Inhibits Cholesterol Absorption But Does Not Affect Acute Hepatic or Intestinal Cholesterol Synthesis in Rats*, British Journal of Pharmacology 138: 1459-1464, 2003.

such as composition (Office Action at pages 3-4). It is alleged that Frei teaches that antioxidants such as vitamins C or E can be useful for inhibiting atherogenesis and normalizing vascular functions. (Office Action at page 4).

In the Office Action, it is further alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the compound of Rosenblum *et al.* with the compound of Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose, citing *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980) (Office Action at page 4). Further, it is asserted that one of ordinary skill in the art would have been motivated to include an antioxidant since vitamin C, an antioxidant, is known to inhibit the development of atherosclerosis (Office Action at pages 4-5).

Rosenblum *et al.* disclose the compound of Formula II (ezetimibe) at page 29, Ex. 6. Rosenblum *et al.* disclose starch-based pharmaceutical compositions including compounds of Formula I of Rosenblum *et al.* (Ex. A and B Page 29). Rosenblum *et al.* teach that the active compounds therein can be combined with HMG CoA reductase inhibitors, such as simvastatin (Page 5, paragraph 0028). Rosenblum *et al.* also disclose that the active compounds are useful for reducing cholesterol and the risk of atherosclerosis (claims). However, Rosenblum *et al.* do not disclose using ezetimibe with aspirin and optionally an antioxidant.

Ullah discloses the use of a combination of aspirin for reducing myocardial infarction and a statin (such as simvastatin) for lowering cholesterol and preventing or treating atherosclerosis at page 1, lines 14-18, in combination. However, Ullah does not disclose using ezetimibe to prevent or treat atherosclerosis, or to use ezetimibe in combination with aspirin and optionally an antioxidant.

Frei discloses that antioxidants may inhibit atherogenesis and improve vascular function by two different mechanisms (Abstract). Lipid-soluble antioxidants present in LDL, such as vitamin C, can inhibit LDL oxidation (Abstract). Antioxidants present in the cells of the vascular wall decrease cellular production and release of reactive oxygen species (ROS), inhibit endothelial activation and improve the biologic

activity of ENDO (Abstract). However, Frei does not disclose using ezetimibe to treat or prevent atherosclerosis, or to use ezetimibe in combination with aspirin and optionally an antioxidant.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Fritch*, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). "It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" *In re Fritch*, 972 F.2d at 1266, quoting *In re Fine*, 5 U.S.P.Q.2d 1596, 1600.

To ensure that the examiner does not use impermissible hindsight, the law requires more than simply picking two references that teach separate components of the claimed invention. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 U.S.P.Q.2d 1385, 1396 (2007)." MPEP (Rev. Sept. 6, 2007) § 2143.01. Thus, some articulated reason with rational underpinning to support the legal conclusion of obviousness must be provided for the Examiner to meet his or her burden. MPEP § 2143.01, *citing KSR Int'l.*, 82 U.S.P.Q.2d at 1396 *quoting In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l.*, 127 S.Ct. 1727, 1741. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does". *Id.* Examples of rationales to support a *prima facie* showing of obviousness are provided in MPEP (Rev. Sept. 6, 2007) § 2143:

> (A) Combing prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teaching to arrive at the claimed invention.

If a *prima facie* case of obviousness is made, an Applicant may rebut the showing of obviousness through secondary considerations such as commercial success, long felt but unsolved needs, failure of others, etc. *KSR Int'l.*, 127 S.Ct. at 1734 (2007), *citing*, *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). "The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, **with due consideration to the persuasiveness of any arguments and any secondary evidence.**" MPEP, (Rev. 1, Feb. 2003) § 716.01(d) (emphasis added) and *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Claims 1 and 47 recite a composition and therapeutic combination, respectively, comprising 0.1 to 1,000 mg of a sterol absorption inhibitor of Formula (II) (ezetimibe); and 1 to 1,000 mg of aspirin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no motivation to combine the claimed components of sterol absorption inhibitor of Formula (II) (e.g., ezetimibe) and aspirin in the specified amounts.

Applicants wish to emphasize that claim 1 does not require the presence of an optional third component, such as a statin.

With respect to patentability of a composition or combination of ezetimibe and aspirin, Rosenblum *et al.* do not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin or in the recited amounts. **Rosenblum *et al.* do not suggest or disclose that the disclosed sterol absorption inhibitors have any effect on platelet aggregation.**

Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Further, in Ullah, aspirin is disclosed as being useful for reducing myocardial infarction at page 1, lines 14-18, **not for treating atherosclerosis.** Ullah does not disclose sterol absorption inhibitors. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. *Id.*

In the Office Action at pages 4 and 5, *In re Kerkhoven* 626 F.2d 846, 205 U.S.P.Q. 1069 (CCPA 1980), was cited as supporting the argument that combining the compositions of Rosenblum *et al.* and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, Ullah does not disclose **aspirin** as being useful for lowering cholesterol or treating atherosclerosis, but rather for treating myocardial infarction. **Therefore, *In re Kerkhoven* does not apply since Ullah does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.**

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin. Even if the teachings of Frei were combined with those of Rosenblum *et al.* and Ullah as suggested in the Final Office Action, one skilled in the art would not be motivated to provide a composition having ezetimibe and blood modifier such as aspirin. *In re Kerkhoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Further, Applicants respectfully request consideration of the evidence set forth in the Declaration by Drs. Davis and Chintala. These results indicate that the combination of ezetimibe with aspirin enhances the ability of aspirin to inhibit platelet aggregation, and combination of ezetimibe and aspirin will prevent vascular complications greater than either agent alone. (Davis Declaration at paragraph 6; Chintala Declaration at paragraph 6). **The above test data provides evidence of unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation when compared to treatment with aspirin alone or ezetimibe alone. None of the cited references, taken alone or combined as set forth in the rejection, suggests or discloses the unexpected synergy of the combination of ezetimibe and aspirin to inhibit platelet aggregation.**

Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. MPEP 716.01(a). The Court of Appeals for the Federal Circuit stated in *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983) that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." MPEP § 716.01(a). Applicants respectfully request that these unexpected results be considered as evidence of non-obviousness in the determination of patentability.

Therefore, the *prima facie* case of obviousness based upon Rosenblum *et al.*, Ullah and Frei has not been established and the rejection of claims 1, 3, 11, 18-20 and 47 should be reconsidered and withdrawn.

If claim 1 is determined to be non-obvious, then all of the claims dependent upon claim 1 also should be determined to be non-obvious.

Claims 35-37 depend from claim 1 and further recite at least one HMG CoA reductase inhibitor, such as simvastatin. Thus, the composition would comprise

ezetimibe and aspirin in the recited amounts, and HMG CoA reductase inhibitor, such as simvastatin.

Applicants wish to emphasize that claim 1 does not require the presence of at least one HMG CoA reductase inhibitor, such as simvastatin.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no motivation to combine the claimed components of ezetimibe, aspirin, in the recited amounts, and HMG CoA reductase inhibitor.

For the same reasons as discussed above, Rosenblum *et al.* and Ullah provide no motivation for a triple combination of ezetimibe, aspirin, and HMG CoA reductase inhibitor. *In re Kerkhoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis. Frei only discloses antioxidants as useful for treating atherosclerosis, and therefore is not relevant to the rejection of these claims. Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis Declaration and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the prima facie case of obviousness based upon Rosenblum *et al.*, Ullah and Frei has not been established and the rejection of claims 35-37 should be reconsidered and withdrawn.

Claims 42-45 depend from claim 1 and further recite at least one antioxidant or vitamin. Thus the composition would comprise sterol absorption inhibitor, aspirin, and antioxidant or vitamin.

Applicants wish to emphasize that claim 1 does not require the presence of a third component, such as a statin.

With respect to patentability of a composition or combination of a sterol absorption inhibitor, aspirin and antioxidant or vitamin (without the presence of a statin), Rosenblum *et al.* does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin. Ullah does not suggest or disclose combinations of a sterol absorption inhibitor and blood modifier such as aspirin.

In Ullah, aspirin is disclosed as being useful for reducing myocardial infarction at page 1, lines 14-18, not for treating atherosclerosis. The statin in Ullah is disclosed as lowering cholesterol and treating atherosclerosis. *Id.*

In the Office Action, *In re Kerkhoven* was cited as supporting the argument that combining the compositions of Rosenblum *et al.* and Ullah, which are known to be useful to reduce cholesterol level and the risk of atherosclerosis individually, into a single composition useful for the very same purpose would be considered obvious.

However, the invention of claim 42 is for a sterol absorption inhibitor, aspirin and antioxidant or vitamin. Ullah does not disclose aspirin as being useful for lowering cholesterol or treating atherosclerosis. *In re Kerkhoven* does not apply since Ullah only discloses aspirin as useful for treating myocardial infarction and does not disclose aspirin as having the same purpose as a cholesterol absorption inhibitor or HMG CoA reductase inhibitor, namely to lower cholesterol and thereby treat atherosclerosis.

Frei does not disclose sterol absorption inhibitors or blood modifiers such as aspirin. Even if the teachings of Frei were combined with those of Rosenblum *et al.* and Ullah as suggested in the final Office Action, one skilled in the art would not be motivated to provide a composition having a having a sterol absorption inhibitor, blood modifier such as aspirin and vitamin or antioxidant.

Applicants respectfully request consideration of the evidence of unexpected results of the combination of ezetimibe and aspirin as set forth in the Davis and Chintala Declarations and as discussed above as evidence of non-obviousness in the determination of patentability.

Therefore, the prima facie case of obviousness based upon Rosenblum *et al.*, Ullah and Frei has not been established and the rejection of claims 42-45 should be reconsidered and withdrawn.

On pages 5-7, the Office Action responds to Applicant's Amendment of January 9, 2007, the Declaration by Drs. Davis and Chintala dated January 3 and 4, 2007 respectively, and the Supplemental Communication dated January 11, 2007. The Office Action contends that "the dosage claimed is not commensurate with the dosage used in the experiment." (Office Action at page 5). Applicants respectfully traverse this rationale because it does not have any application to a rejection under 35 U.S.C. § 103. Rejections under Section 103, which is the only pending rejection on record, are limited to assertions that the claimed invention is obvious in view of the prior art. The Office Action asserts that "there is no rationale as to how the dosage of ezetimibe can be expanded to a broad range as claimed. The rationale for expanding the dosage of aspirin is not convincing." (Office Action at page 5). However, neither of these assertions claim that the dosage range is obvious in view of a cited reference.

Notwithstanding the above, Dr. Chintala's Declaration supports the claimed dosage range. To determine if sufficient information is provided to claim a particular element, one must inquire whether the claimed invention can be practiced without undue experimentation. MPEP § 2164.01. That some experimentation may be required is not fatal because the issue is whether the experimentation is undue. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991). As Dr. Chintala's Declaration establishes, there is no additional experimentation required to arrive at the claimed dosage range. The Declaration establishes that the dose of aspirin varies in humans from 100 mg/day to 1000 mg/day; therefore, it is reasonable to assume that a therapeutic dose of aspirin is in the range of 1-1000 mg/day. (Chintala Declaration at paragraphs 7-8). The Declaration further establishes that the dose of ezetimibe is "3 mg/kg/day, which was previously found to be the maximally effective dose to prevent diet-induced hypercholesterolemia in rats;" therefore, an ezetimibe dosage range from 0.1-1000 mg/day in humans should be clinically effective. (Chintala Declaration at paragraph 9).

See *Cross v. Iizuka*, 224 U.S.P.Q. 739 (Fed.Cir 1985) (holding that if an assay to determine dosage is known to a skilled artisan, the dosage can be determined without undue experimentation).

On page 6, the Office Action asserts that "the motivation to combine the teachings of the cited prior art is based on the fact that the herein claimed agents are known to be useful in reducing the risk of cardiovascular diseases such as atherosclerosis." The motivation purportedly is that the claimed agents "have the same therapeutical use in the art." (Office Action at page 6). Applicants respectfully traverse this assertion.

As stated above, to ensure that the examiner does not use impermissible hindsight, the law requires more than simply picking two references that teach separate components of the claimed invention. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, 82 U.S.P.Q.2d 1385, 1396 (2007)." MPEP (Rev. Sept. 6, 2007) § 2143.01. Thus, some articulated reason with rational underpinning to support the legal conclusion of obviousness must be provided for the Examiner to meet his or her burden. MPEP § 2143.01, *citing KSR Int'l.*, 82 U.S.P.Q.2d at 1396 *quoting In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006).

Supplementing the above reasons, there is no motivation to combine the cited reference because there is no recited motivation to substitute the statin discussed in Ullah with the claimed sterol absorption inhibitor, to add a sterol absorption inhibitor to the compounds taught in Ullah, or to substitute the statin discussed in Ullah with the claimed sterol absorption inhibitor and add antioxidants or vitamins. *See Ex parte Wolk*, 2007 WL 1277911 (BPAI, April 30, 2007).

In *Wolk*, the Board held that the examiner incorrectly applied *In re Kerkhoven*. *Id.* at *3. The *Wolk* patent claimed an electroluminescent composition and an organic electronic device. *Id.* at *2. The electroluminescent composition included a

charge transporting, charge blocking, light emitting and/or color conversion material. *Id.* at *2. The organic electronic device was a polymeric material having an aromatic radical. *Id.* at *2.

The *Wolk* claims were rejected under Section 103 as unpatentable over Mori in view of Burroughes and Hosokawa. *Id.* at *1. The rejection asserted that Hosokawa taught the claimed electroluminescent composition, and that Burroughes taught the claimed polymer. *Id.* at *2. Even though Mori failed to teach the two claimed compounds, the examiner in *Wolk*, nevertheless, claimed that it provided motivation to combine Burroughes and Hosokawa. *Id.* at *1-2. The issue in *Wolk* was whether "the examiner furnished an adequate reason (motivation) for one of ordinary skill in the art to combine the light emissive F&BT polymer of Burroughes with the light emissive A-7 compound of Hosokawa for forming a mixed luminescent layer of a light emitting device according to Mori and in a manner that would have rendered the subject matter of representative claim 1 *prima facie* obvious?" *Id.* at *2.

The Board found that the examiner failed to explain how and where Mori furnished direction or motivation to combine compounds taught in Burroughes and Hosokawa. *Id.* at *2-3. Particularly, the Board held that the examiner's reliance on *In re Kerkhoven* was misplaced because the examiner failed to "articulate why one of ordinary skill in the art would discount the teachings of Mori as to using oxidation potential and reduction potential criteria for selecting materials to be part of the luminescent layer" *Id.* at *3. In summary, according to *Ex parte Wolk*, an examiner may not solely rely on *In re Kerkhoven* as the motivation for combining two compounds.

Likewise, the instant Office Action fails to provide any motivation to substitute Ullah's statin with ezetimibe in the claimed amounts and fails to provide any motivation to combine ezetimibe with aspirin. On page 6, the Office Action contends that "the basis is rather [the agents] are known to have the same therapeutical use in the art." Just like in *Ex parte Wolk*, this alone is insufficient to provide motivation for a skilled artisan to combine the references, particularly when sterol absorption inhibitors were known at the time that Ullah was filed, yet Ullah provides no express or implicit

motivation to substitute statins with sterol absorption inhibitors. Ullah's failure to provide any motivation to use sterol absorption inhibitors instead of statins evidences that the claimed composition is not obvious to a skilled artisan unless some reason can be provided explaining how that in 1998, the claimed invention was not obvious (in view of the fact that Ullah, being one skilled in the art, failed to disclose using sterol absorption inhibitors), but less than four years later, the combination became obvious.

Moreover, Ullah and Rosenblum *et al.* are directed to two different ailments. *In re Kerkhoven* states that the two compositions must be used for the same purpose. Here, Ullah's aspirin and statin combination is used for reducing myocardial infarction, which is a different purpose from the purpose for Rosenblum *et al*'s ezetimibe (reducing cholesterol and the risk of atherosclerosis). Since these differing purposes are not resolved by some motivation to combine the references, prima facie obviousness has not been established. The mere fact that aspirin may have been known to treat myocardial infarction does not make it obvious to combine aspirin with a cholesterol treatment.

Conclusion

Accordingly, Applicants respectfully request that the § 103(a) rejection of claims 1, 3, 11, 18-20, 35-37, 42-45 and 47 be reconsidered and withdrawn. Also, Applicants respectfully request rejoinder and allowance of claims 38-41 withdrawn by restriction, which were timely traversed, and claim 46.

Respectfully submitted,

Date: **December 4, 2007**

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